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EXAMINER	
SALMON, KATHERINE D	
ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/659,519	SIDRANSKY ET AL.	
	Examiner	Art Unit	
	KATHERINE SALMON	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12 and 14-24* is/are pending in the application.

4a) Of the above claim(s) *20-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12 and 14-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed 4/25/2008. Claims 12, 14-24 are pending.

2. Claims 20-24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 6/15/2006.

3. The rejections present below for Claims 12 and 14-19 are newly applied. It is noted that the 35 USC 112/Scope of Enablement presented in the non-final action (1/28/2008) has been changed to a full lack of enablement. Response to arguments follows.

4. This action is Non-FINAL.

Withdrawn Objections/Rejections

5. The objection to priority and the oath made in section 6-7 of the nonfinal action (1/28/2008) is moot based upon amendments to the claims.

6. The rejection of the claims under 35 USC 112/second paragraph, second paragraph made in section 8 of the previous office action is moot in view of the amendments to the claims.

Claim Rejections - 35 USC § 112/ Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. The following rejection has been changed from the Scope of Enablement presented in the non-final rejection (1/28/2008); however, this change was necessary to address the amendments to the claims presented 4/25/08. Further since the claim has been amended to no longer require a methylation steps, the claim has been interpreted to correlate the deletion of exon 1 with any cell proliferative disorder and therefore the issues concerning methylation steps in the non-final of 1/28/2008 have been removed. Response to arguments follows.

8. Claims 12 and 14-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claim 1 is drawn to a method of detecting cell proliferative disorder comprising contacting a sample comprising RNA with oligonucleotide primers that permit extension of a sequence complementary to a polynucleotide sequence encoding exon 1 of p16 gene and a sequence complementary to a polynucleotide sequence encoding exon 2 of the p16 gene, amplifying the resulting extension products comprising contacting the extension products with a sense oligonucleotide which binds within and extends sequences from a 5' ALT gene and determining the presences of an amplification product that encodes a truncated p16 gene product lacking exon1, comprising detecting a first amplification product containing exon 2 of the p16 gene in the absence of identifying a second amplification product containing exon 1 of the p16 gene wherein the presence of the truncated p16 gene product is associated with a cell proliferative disorder. Claims 14-15 define the sample. Claim 16 is drawn to a method wherein the truncated of the p16 gene is indicative of a neoplasm. Claim 17 defines the neoplasm. Claim 18 define the sample. Claim 19 defines the amplification reaction.

Therefore the claims encompass a method for detecting and correlating the absence of exon 1 with any type of cell proliferative disorder in any sample. The claims therefore are drawn to the correlation of any fragment of exon 1 being absent in the sample as being correlative to the detection of any cell proliferative disorder.

Nature of the Invention

The claims encompass method for detecting any fragment of exon 1 and 2 and the association of the lack of exon1 with any cell proliferative disorder.

The invention is in a class of invention, which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Guidance in the Specification

The specification asserts that the p16 gene has been identified as a region having homozygous deletions in many tumors and that the 5' ALT is shown to be about 30 kb upstream for p16 (p. 5 lines 6-9).

The specification asserts that homozygous deletions are frequent in breast and renal cell but are not commonly associated with colon and prostate (p. 10 1st paragraph). The claims are drawn to the detection of any cell proliferative disorder which the presence of the truncated p16 gene (e.g. the absence of exon 1) indicates a cell proliferative disorder. However, the instant specification asserts that deletions are not associated with colon and prostate cell lines and therefore the specification shows unpredictability for performing the method as broadly claimed.

The specification asserts that the 5'ALT of the invention is derived from a mammalian organism and most preferably from a human (p. 14 2nd paragraph). The claims are drawn to the determination of a truncated p16 in any species including platypus, dogs, horses, and humans. The instant specification has not provided guidance the same truncated p16 gene is observed in any mammalian species and therefore it is unpredictable to correlate detection of any cell proliferative disorder in any species.

The specification asserts a method for detecting a cell proliferative disorder comprising contacting a cellular compound with a reagent which detects an alteration in p16 (p. 41 last paragraph). The specification asserts that the gene encoding the tumor suppressor p16 has been found to be deleted in certain cancers (p. 43 last paragraph). The instant specification asserts a method of detecting the presence or absence of all or particular regions of the human chromosome 9p21 (p. 44 1st paragraph).

The instant specification has not defined cell proliferative disorder and therefore can be broadly interpreted as any disorder which causes cell proliferation including bladder cancer, breast cancer, and renal cancer. The instant specification discloses that deletions are not observed in some cancer types including colon and prostate (p. 10 1st paragraph). Therefore the specification does not provide guidance for the detection of any cell proliferative disorder.

The claims are drawn to the detection of an absence of exon 1, which would include an absence in only one allele. The specification asserts, however, the detection of homozygous deletion. Therefore there is no guidance for the detection of

hemizygous deletion as is claimed. Therefore it is unpredictable that hemizygous deletion is correlative to cell proliferative disorder without the skilled artisan performing undue experimentation.

The specification asserts that when the 5' ALT gene is spliced into the region right before exon 2 then the product of exon is not amplified (paragraphs 135-136). Therefore the specification indicates that the specific amplification of the entire exon 1 and 2 region is affected because the 5' ALT gene splices into the sequence and therefore the two specific primers used can not amplify the exon 1 region and the exon 2 region. The claims, however, are broadly drawn to amplification of any exon 1 or 2 region; it is unpredictable that the insertion of the 5' ALT gene into the p16 gene would affect the amplification of any region of the exon 1 or 2 by any primer.

The instant specification asserts the role of 5'ALT in forming alternate transcripts and truncated p16 indicates that an excessive level of kinases can develop within cells that harbor 5'ALT gene deletions or polymorphisms that comprise the ability of p16 to inhibit CDK4 (p. 44 2nd paragraph). However, the instant specification has not specifically defined truncated p16 gene. Therefore it is unclear if the truncated p16 gene only lacks exon 1 or if the truncated p16 gene encompasses the deletion of other regions.

The claims are broadly drawn to a method of detecting any cell proliferate disorder in any sample by detection of a product which lacks exon 1. However, the specification does not show guidance for the claim as broadly written. The specification discloses that deletions of exon 1 are not correlative to some cell proliferative disorders.

Further, such associations are drawn to homozygous deletion of exon 1 wherein the claims are drawn to any deletion (e.g. homozygous or hemizygous). As discussed below the examples in the specification do not provide support for the claim. As shown below, the specification discloses that homozygous deletions are only observed in a few cancer cell lines, not as claimed in any sample, which would include tumor samples. As discussed below, the art teaches that unpredictable to correlate the absence of exon 1 in the p16 gene with any cell proliferative disorder in any sample. It is therefore unpredictable to practice the invention as claimed.

Working Examples

The examples provided by the specification, fail to provide guidance as to the

Example 1 part 1: The specification asserts cells from head and neck cancer cell lines, lung cancer cell lines, pancreatic adenocarcinomas cell lines were extracted (p. 47 last paragraph).

Example 1 part 2 and 3: The specification asserts fragments of exon 1, 2, and 3 were amplified (p. 48 and 49).

Example 4: The specification asserts the complete p16 and p16-5'ALT cDNA was amplified by RT-PCT (p. 57 1st full paragraph). The specification asserts that immunopreciptation was performed in which anti-p16 antibodies which recognize either the C-terminus or the N-terminus (p. 57 1st full paragraph). The specification asserts that the N-terminal antibody was not recognized indicating that the product lacked the N-terminal exon 1 coding sequence (p. 57 1st full paragraph).

Example 6: Table 1 presents 5' CpG island methylation related to allelic status and sequence analysis of the p16 in the cell lines. The p16 sequence indicates the majority of the primary human cancers have the wild-type p16 sequence (p. 61). This indicates p16 with exon 1 present (wild type) would be observed in primary human cancers, therefore it is unpredictable to make an association of a mutant p16 gene (absent of exon 1) with cancers.

Example 8: This working example is drawn to methylation steps which are not encompassed by the instant claims.

Example 11: The specification asserts Exon 1 of p16 lies in a CpG island which is unmethylated in normal tissue (p. 67 1st full paragraph). Table 2 shows inactivation of p16 in cell lines and primary tumors (p. 69). Table 2 discloses that in cell lines only breast and renal cancer have homozygous deleted p16 exon1 genes (p. 69). Table 2 discloses that none of the primary tumors which include samples from breast, colon adenoma, and colon cancer have homozygous deleted p16 (p. 69). Therefore the specification discloses that in many samples such as primary tumors and some cell lines there is no correlation of cell proliferative disorder and the absence of exon 1 in the p16 gene product.

The unpredictability of the art and the state of the prior art

The art teaches that p16 deletion of exon 1 is not correlative to the detection of any cell proliferative disorder. Moulton et al. (American Journal of Pathology March 1995 Vol 146 p. 613) teaches the detection of p16 in gliomas tumors (abstract).

Moulton et al teaches that p16 deletions are not detected in low grade gliomas (abstract). Therefore Moulton et al teaches that deletions of p16 are not correlative to detection of certain gliomas.

Li et al. (International Journal of Oncology 1995 Vol. 7 p. 257) teaches that MTS1 (e.g. p16) deletions are found in esophageal carcinoma cell lines but not in primary carcinomas of the human esophagus (abstract). Li et al. teaches that of the 21 primary squamous cell carcinomas of the esophagus no deletion was found in exon 1 (p. 259 1st column 2nd paragraph). Therefore Li et al. teaches that deletions in the p16 gene are not found in primary carcinomas such as human esophagus.

Huang et al. (Cancer Research 1996 Vol 1137 p 1137) teaches detection of detections of the P16 gene in ducal pancreatic carcinoma from a patient and from pancreatic carcinoma cell lines (abstract). Huang et al. teaches that alterations in p16 occur more frequently in tumor derived cell lines than in primary ductal carcinomas (p. 1140 2nd column last paragraph).

Therefore the art as shown by Li et al. and Huang et al., show that for many primary tumors such as human esophagus carcinomas and primary ductal carcinoma there is no correlation between detection of cell proliferative disorder and the absence of exon 1 of the p16 gene. Further, Moulton et al. teaches that in samples wherein the exon 1 is deleted it is unpredictably depending on the grade of the tumor. For example the deletion is correlated to gliomas tumors but not detectable in low grade glioma tumors. Therefore the art does not provide guidance to detect any cell proliferative disorder in any sample by the detection of the absence of exon 1 in the p16 gene.

Quantity of Experimentation

The quantity of experimentation in this area would be extremely large since there is significant number of parameters that would have to be studied. To practice the invention as broadly as it is claimed, the skilled artisan would have to determine the correlation of the deletion of exon 1 in the p16 gene with any cell proliferative disorder in any sample of any mammalian species.

The skilled artisan would need to perform undue experimentation to detect a cell proliferative disorder because both the art and the instant specification teach that detection of exon 1 of the p16 is not observable in many primary tumors and cell lines.

To use the invention as presented would require a large amount of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v*

Novo Nordisk 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

Thus the applicants have not provided sufficient guidance to enable a skilled artisan to make the claimed invention in a manner reasonably correlated with the claimed method of detection a cell proliferative disorder. Further the specification does not provide guidance to the correlation of any cell proliferative disorder in any sample. The skilled artisan would have to perform undue experimentation to determine correlation of the absence of exon 1 of the p16 gene to detection of cell proliferative disorder.

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the negative teachings in the art, and the lack of guidance provided in the specification balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

The reply traverses the rejection. A summary of the arguments in the reply and response to arguments is presented below.

The reply asserts that the claims have been amended to incorporate limitations as suggested by the examiner (p. 7 1st paragraph). The reply asserts that the claim have been amended to clarify that the methods are directed towards detecting a cell

proliferative disorder and that the specification shows support of this in Example 4, Example 6, Example 8, and Example 11 (p. 7 1st paragraph).

These arguments have been fully reviewed and are not found persuasive.

Though the claims have been incorporated to include limitations as suggested by the examiner, the claims as amended still encompass enablement issues with regard to correlation of the absence of exon 1 with detection of a cell proliferative disorder as claimed.

The reply asserts that Examples 4, 6, 8, and 11 disclose support fro the claimed method. However, as discussed above none of the examples disclose the correlation of the absence of exon 1 in the p16 gene to any cell proliferative disorder in any sample. Further, Example 11 discloses the unpredictability of the claimed invention. In Example 11, the specification asserts Exon 1 of p16 lies in a CpG island which is unmethylated in normal tissue (p. 67 1st full paragraph). Table 2 shows inactivation of p16 in cell lines and primary tumors (p. 69). Table 2 discloses that in cell lines only breast and renal cancer have homozygous deleted p16 exon1 genes (p. 69). Table 2 discloses that none of the primary tumors which include samples from breast, colon adenoma, and colon cancer have homozygous deleted p16 (p. 69). Therefore the specification discloses that in many samples such as primary tumors and some cell lines there is no correlation of cell proliferative disorder and the absence of exon 1 in the p16 gene product. Therefore the instant specification has not provided guidance to use the claimed method.

Conclusion

9. No claims are allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Katherine Salmon whose telephone number is (571) 272-3316. The examiner can normally be reached on Monday-Friday 8AM-430PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Katherine Salmon/
Examiner, Art Unit 1634

/Ram R. Shukla/

Supervisory Patent Examiner, Art Unit 1634